IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re Application of: | ( | Art Unit: 1615 |
| Katsuya MATSUDA et al | ( | Examiner: P. KULKOSKY |
| Application No.: 09/807,190 | ( | Confirmation No. 4190 |
| Filed: April 10, 2000 | ( | Washington D.C. |
| For: POLYMER COMBINING WITH PHOSPHORIC ACID AND PREPARATION CONTAINING THE SAME | ( | March, 2003 |

DECLARATION UNDER CFR 1.132

Honorable Commissioner for Patents and Trademarks,

Washington, D.C. 20231

Sir:

I, Katsuya MATSUDA, declare and state that I am one of the applicants of the above-identified patent application.

I declare that I graduated in March 1981 from the Faculty of Technology, Keio University, Yokohama, Japan and that I received a bachelor degree in Engineering from the same University.

I declare further that I have been employed by Chugai Seiyaku Kabushiki Kaisha, the assignee of the present application, since 1981, and that I have been engaged as a researcher into solid dosage formulations.

I declare further that I am a Senior Researcher at Formulation Technology Research Dept. of the Assignee.

I declare further that I have read all of the Official

Actions in the above-identified application, and have read and am familiar with each of the references cited in the Official Action by the Examiner.

I declare further that the following test was conducted at my direction or under my supervision, and that the test results are true and correct to the best of my knowledge.

[Purpose of the Test]

A phosphate-binding polymer useful in treating hyperphosphatemia is administered in a high single dosage amount of 1-2 g, and the patients to be treated, who are undergoing dialysis, include a high proportion of elderly persons who tend to have difficulty swallowing tablets. Thus, it is important to reduce a stickiness of tablets containing the polymer on oral mucosa to make oral administration easy. In addition, it is desired to reduce the stickiness from a viewpoint of formulation of the polymer into tablets.

In order to review stickiness of tablets in oral cavity on oral mucosa and stickiness between tablets, tablets are formulated from the phosphate-binding polymer under the conditions described below, and tested to evaluate stickiness thereof.

[Test Method]

Poly(allylamine) was subjected to a crosslinking reaction with epichlorohydrin to obtain crosslinked polymer. The dried polymer was ground to powder of a phosphate-binding polymer. With 200 mg of the polymer (a moisture content of 7.9%; a ratio of particles having a size of 300 $\mu$m or less being 100%), was mixed with 100mg of one of additives, crystalline cellulose (Avicel TM PH101 manufactured by Asahi Chemical Industry Co., Ltd.) and low substituted hydroxypropyl cellulose (L-HPC LH31 manufactured by Shin-Etsu Chemical Co., Ltd.), hydroxypropyl cellulose (HPC-L manufactured by Nippon Soda Co., Ltd.) and hydroxypropylmethyl cellulose 2910 (HPMC TC-5-RW manufactured by Shin-Etsu Chemical Co., Ltd.). The obtained mixture was compressed under a static pressure of 1000kg to give a tablet (diameter: 10 mm) weighing 300 mg.

For comparison, 300 mg of the phosphate-binding polymer, without an additive, was compressed under the same conditions to give a tablet.

Hardness of the obtained tablets was measured by a hardness tester (Pharmatest). The results are shown in Table 1 below. Further, to forecast stickiness of the tablets in oral cavity, about 3% by weight of water based on the weight of a tablet was sprayed on both

sides(surfaces) of each of two tablets and they were superposed to each other. The stickiness between the two tablets was evaluated, and the results are also shown in Table 1.

[Results]

Table 1: Relation between kind of additive and tablet hardness or tablet stickiness

| No. | Tablet Composition | | Tablet hardness (KP) | Stickiness |
|---|---|---|---|---|
| 1 | Polymer | 300mg | 6.2 | sticky |
| 2 | Polymer<br>Crystalline Cellulose | 200mg<br>100mg | 8.6 | not sticky |
| 3 | Polymer<br>L-HPC | 200mg<br>100mg | 7.4 | not sticky |
| 4 | Polymer<br>HPC-L | 200mg<br>100mg | 19.1 | sticky |
| 5 | Polymer<br>HPMC | 200mg<br>100mg | 7.5 | sticky |

Tablets containing only the phosphate-binding polymer exhibited stickiness between tablets.

Tablets containing HPC-L or HPMC (Nos. 4 and 5) exhibited stickiness between tablets, but tablets containing crystalline cellulose or L-HPC did not exhibit stickiness. Please refer to the attached photographs indicated as Fig.1 and Fig. 2.

During formulation of coated tablets which can be more easily administered, it is necessary to prevent uncoated tablets from adhering to each other in a spraying step to produce twin tablets. According to the present invention,

desired coated tablets of the phosphate-binding polymer can be obtained by using a specific additive. It is confirmed that a combination of the phosphate-binding polymer of the present invention with a specific additive such as crystalline cellulose or L-HPC exhibits unexpectedly good effects.

Fig. 1 Before Stickiness Test

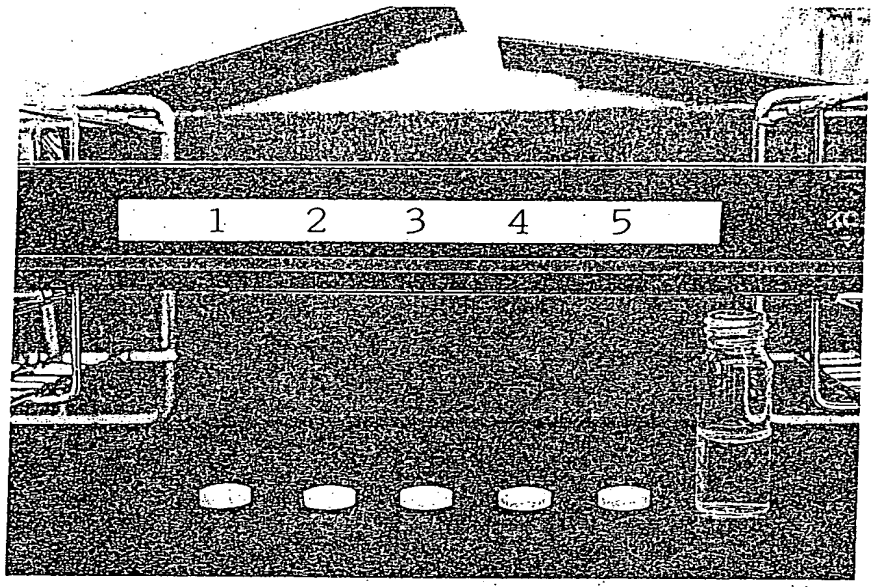
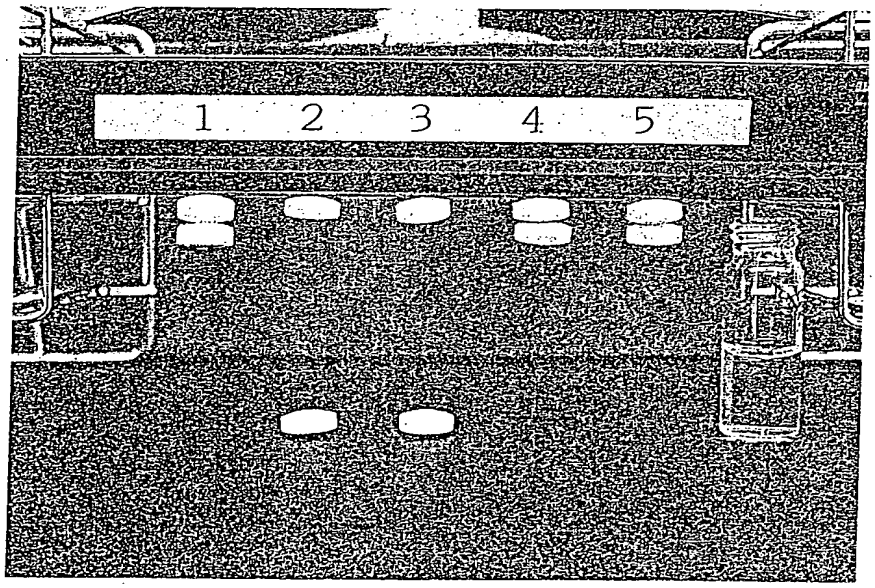



Fig. 2 Results of the Stickiness Test



I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated this th day of February, 2005

By: _____
Katsuya Matsuda